



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :  
SHIMIZU et al. :  
Serial No. 10/017,755 : Group Art Unit 1615  
Filed on October 30, 2001 : Examiner TRAN, Susan T  
For ORALLY DISINTEGRABLE TABLETS

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner of Patent and Trademarks, Washington, D.C.

Sir,

I, Toshihiro SHIMIZU, declare:

That I am a citizen of Japan residing at 15-3, Aramakiminami 2-chome, Itami-shi,  
Hyogo, Japan;

That I was born on July 10, 1964 in Okayama, Japan;

That I graduated from Gifu Pharmaceutical University, with degree of Bachelor of  
Pharmaceutical Science in March 1988;

That I have been employed by Takeda Chemical Industries, Ltd., Osaka, Japan,  
since April, 1988, and have been engaged in research and development in the  
Pharmaceutical Production Division of said company;

That I have been appointed a Research Head of Pharmaceutical Technology  
Research & Development Laboratories in said Pharmaceutical Production Division since  
2004;

That I am a member of the Pharmaceutical Society of Japan, and have published,  
with other research workers, a number of reports on scientific studies, among others,  
including

1. Shimizu T., Nakano T., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 942-947 (2003)
2. Shimizu T., Kameoka N., Iki H., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1029-1035 (2003)
3. Shimizu T., Sugaya M., Nakano Y., Izutsu D., Mizukami Y., Okochi K., Tabata T.,

Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1121-1127 (2003) ;

That I am one of the co-inventors of the United States Patent Application Serial No. 10/017,755 filed on October 30, 2001;

That the following Experiment was conducted by myself and under my supervision and control:

Test for Evolved CO<sub>2</sub> Tolerability in Human Volunteers

1. Calculation of what amount of CO<sub>2</sub> is theoretically evolved according to Examples of U.S. Patent No. 6,132,770

I calculated what amount of CO<sub>2</sub> is theoretically evolved according to Examples of U.S. Patent No. 6,132,770.

Ingredient	Molecular weight
Citric acid anhydrous	192.12
Sodium carbonate anhydrous	105.99
Sodium bicarbonate	84.01

- 1 Mol of citric acid anhydrous reacts with 3 mol of sodium carbonate anhydrous to produce 3 mol of carbon dioxide.
- 2 Mol of citric acid anhydrous reacts with 2 mol of sodium bicarbonate to produce 3 mol of carbon dioxide.

Example 1

Ingredient	Content / 1 tablet	mmol	Volume of carbon dioxide to be evolved	Total volume of carbon dioxide to be evolved
Citric acid anhydrous	0.605g	3.15mmol	—	128.3ml
Sodium carbonate anhydrous	0.036g	0.34mmol	7.6ml	
Sodium bicarbonate	0.453g	5.39mmol	120.7ml	

Example 3

Ingredient	Content / 1 tablet	mmol	Volume of carbon dioxide to be evolved	Total volume of carbon dioxide to be evolved
Citric acid anhydrous	1.287g	6.70mmol	—	273.3ml
Sodium carbonate anhydrous	0.095g	0.90mmol	20.0ml	
Sodium bicarbonate	0.950g	11.31mmol	253.3ml	

Example 4

Ingredient	Content / 1 tablet	mmol	Volume of carbon dioxide to be evolved	Total volume of carbon dioxide to be evolved
Citric acid anhydrous	1.290g	6.70mmol	—	273.6ml
Sodium carbonate anhydrous	0.095g	0.90mmol	20.0ml	
Sodium bicarbonate	0.951g	11.32mmol	253.6ml	

#### Example 5

Ingredient	Content / 1 tablet	mmol	Volume of carbon dioxide to be evolved	Total volume of carbon dioxide to be evolved
Citric acid anhydrous	1.290g	6.70mmol	—	273.6ml
Sodium carbonate anhydrous	0.095g	0.90mmol	20.0ml	
Sodium bicarbonate	0.951g	11.32mmol	253.6ml	

#### Example 6

Ingredient	Content / 1 tablet	mmol	Volume of carbon dioxide to be evolved	Total volume of carbon dioxide to be evolved
Citric acid anhydrous	1.293g	6.73mmol	—	274.4ml
Sodium carbonate anhydrous	0.096g	0.91mmol	20.4ml	
Sodium bicarbonate	0.953g	11.34mmol	254.0ml	

## 2. Test for Evolved CO<sub>2</sub> Tolerability in Human Volunteers

### Method and Results

The suitable amounts of citric acid anhydrous and sodium bicarbonate as effervescent constituents were weighed and mixed so as to produce 10-100 ml of carbon dioxide theoretically. The mixture was held in the mouth for 1 minute without water to produce carbon dioxide, and then spat out, and the mouth was rinsed.

Three human volunteers (A, B and C) evaluated the feelings (sensation) against production of carbon dioxide in the oral cavity.

The results of the evaluation are shown below.

Citric acid anhydrous	Sodium bicarbonate	Volume of carbon dioxide to be evolved theoretically	A	B	C
28.6mg	37.5mg	10ml	△	△	△
57.2mg	75.0mg	20ml	x	x	x
143mg	187.5mg	50ml	x	x	x
286mg	375mg	100ml	x	x	x

○ : no problem, △: tolerable, x: intolerable

Conclusion:

In this test, humans were able to tolerate about 10 ml of carbon dioxide in the oral cavity, but amounts greater than 10 ml were intolerable.

Because the holding time of effervescent constituents in the mouth was only 1 minute, the reaction for producing carbon dioxide have not been completed, therefore calculated volume of carbon dioxide would not have been evolved.

This experiment shows that the uncomfortable large amount of carbon dioxide would be evolved if an effervescent tablet described in any Examples of U.S. Patent No. 6,132,770 is taken orally without water.

It is declared by the undersigned that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 6<sup>th</sup> day of October, 2004.

Toshihiro Shimizu

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